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Incidence of Supraventricular Arrhythmias during Autologous Peripheral Blood Stem Cell Transplantation

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A B S T R A C T

Arrhythmias, especially supraventricular arrhythmias, often complicate the clinical course during autologous hematopoietic cell transplantation (AHCT). We wanted to determine the incidence and risk factors for cardiac arrhythmias during AHCT. The study included 983 patients (median age, 58 years [range, 19 to 77]; 61% male) who underwent AHCT between August 2006 and December 2010 at a single institution and for whom all relevant medical records were available for review. AHCT was done for plasma cell disorders in 58% patients and for lymphoma or leukemia in the remaining. Overall, 92 patients (9.4%) developed a supraventricular tachyarrhythmia at a median of 9 days posttransplantation (range, 0 to 18) and with a median duration of less than 1 day (range, <1 to 17 days). Atrial fibrillation was the most common and seen in 71 patients (7%), followed by atrial flutter and supraventricular tachycardia in 12 (1%) and 8 (1%) patients, respectively. In multivariate analysis, age older than 63 years, presence of premature supraventricular complexes or atrioventricular conduction delay on pretransplantation electrocardiogram, and history of any prior arrhythmia increased the risk of arrhythmia. Development of arrhythmia resulted in longer outpatient follow-up after AHCT, with the median follow-up for those developing an arrhythmia of 22 days compared with 19 days for the rest; $P < .001$. In conclusion, 9% of patients undergoing ASCT developed supraventricular arrhythmias posttransplantation, and this risk was elevated among older patients, those with a prior history of arrhythmias, and those with pretransplantation electrocardiographic abnormalities.

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INTRODUCTION

Autologous hematopoietic cell transplantation (AHCT) has become the standard of care for a variety of malignancies and is also increasingly used for non-malignant acquired disorders. Among more than 50,000 first hematopoietic stem cell transplantations reported for 2006 worldwide, the leading indications were lymphoproliferative disorders (54.5%), leukemia (33.8%), solid tumors (5.8%), and nonmalignant disorders (5.1%) [1]. Most of these transplantations were performed in either Europe (48%) or North America (36%), with AHCT constituting the majority. In the United States, AHCT is performed most commonly for multiple myeloma followed by the lymphomas. Although the process has become considerably safer over the past 2 decades, high-dose chemotherapy and AHCT can be associated with significant morbidity related to a variety of side effects [2-4].

One of the more serious complications of AHCT remains cardiac toxicity. With the use of conventional pre-AHCT clinical cardiac evaluation, major cardiotoxic events such as heart failure, cardiac tamponade, and life-threatening cardiac arrhythmias have been reported to be uncommon, occurring in less than 1% of patients [5]. Arrhythmias, especially supraventricular arrhythmias, however, more commonly complicate the clinical course of these patients [6-9]. This has been clear since the initial report in 1998 by Olivieri et al., who reported 5 cases of atrial fibrillation (AF) in stem cell transplantation recipients after high-dose melphalan [10]. Subsequent studies reported the occurrence of supraventricular arrhythmias in 4% to 10% of bone marrow transplant recipients [6-9]. However, factors predisposing to such arrhythmias have not been well studied to date.

Although these arrhythmias are easily treatable in most patients, they can still result in prolongation of hospital stay and an increased rate of intensive care admissions. We undertook this study to determine the incidence and risk factors for cardiac arrhythmias during AHCT.

METHODS

Following the approval from the Mayo Clinic Institutional Review Board, we retrospectively analyzed the medical records of 1000 consecutive patients who underwent AHCT for various malignancies between August 2006 and December 2010. All patients had given informed consent for the use of their records for research purposes. Seventeen patients who had AHCT for nonhematological malignancies and those who had incomplete information regarding various parameters described below were excluded, leaving 983 patients who met the criteria. Twenty-two of these 983 patients received a combination of marrow and peripheral blood stem cell graft, and all other patients received peripheral blood stem cells only. These patients were managed by multidisciplinary teams on an outpatient basis and were admitted to hospital as and when indicated [11]. Patients were seen on a daily basis, or more often if needed, with daily monitoring of complete blood count and chemistry with replacement of electrolytes and transfusions as clinically indicated. Patients were not routinely placed on cardiac monitoring of any nature irrespective of prior cardiac history.

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Table 1
Baseline Characteristics

Characteristic	N	Percent
Patients	983	—
Age, yr (range)	58 (19-77)	
Gender, men	603	61
Disease		
Acute leukemia	10	2
Amyloidosis	140	14
Hodgkin disease	63	6
Myeloma	404	41
Non-Hodgkin lymphoma	337	34
POEMS	29	3
Conditioning		
BEAM	395	40
Busulfan + cytoxan	3	.3
Cytoxan + TBI	10	1
Melphalan	565	58
ThioTEPA/BCNU (Carmustine)	1	.1
Zevalin/melphalan	8	.8
Medical comorbidities		
Hypertension	372	37.8
CAD	75	7.6
Diabetes mellitus	105	10.6
Hypothyroidism	114	11.6
Hyperthyroidism	2	.2
Renal insufficiency	152	15.5
COPD	27	2.7
Obstructive sleep apnea	70	7.1

POEMS indicates polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes; BEAM, carmustine (BCNU), etoposide, adriamycin, melphalan; TBI, total body irradiation; BCNU, Carmustine; COPD, chronic obstructive pulmonary disease.

For all patients, the medical records were reviewed for age, sex, height, weight, and clinical risk factors for atrial arrhythmia, including presence of systemic hypertension, diabetes mellitus, coronary artery disease (CAD), valvular heart disease, and thyroid diseases. Information regarding history of arrhythmia was obtained from the medical records. Additionally, we also reviewed the electrocardiographic records in our Mayo EKG Database for any reports of arrhythmias or conduction abnormalities. All patients also underwent transthoracic echocardiography before transplantation. The echocardiographic data were electronically retrieved and reviewed for parameters that could affect the risk of arrhythmias such as left ventricular diastolic dysfunction, left ventricular ejection fraction, indexed left atrial volume index, and valvular lesions.

Logistic regression was used to identify the best cut-point for continuous variables, associated with the maximum risk of developing an arrhythmia. The Kaplan-Meier method was used to estimate the median time to onset of any arrhythmia, with patients not developing any arrhythmia censored at the time of dismissal home post-AHCT. The Cox proportional hazards model was used to estimate the risk associated with various baseline factors. Patient-related variables included age; gender; diagnosis; history of coexisting illnesses, such as CAD, hypertension, and diabetes; prior history of arrhythmias; antiarrhythmic medications; or beta-blocker use.

Cardiac parameters examined included left ventricular ejection fraction, left atrial size, or presence of valvular abnormalities on echocardiogram, PR interval, QTc interval, supraventricular complexes, or atrioventricular (AV) conduction delays/blocks that included first- and second-degree AV blocks on pretransplantation electrocardiogram (ECG).

Transplantation-related factors examined include position of central line tip (right atrium versus superior vena cava), conditioning regimen, neutropenic fever, hypokalemia in the posttransplantation period, development of mucositis, and diarrhea. All baseline variables were evaluated, and those found to be significantly associated with arrhythmia at $P < .05$ on univariate analysis were then considered for multivariate analyses. All analyses were performed using JMP 9.03 software (SAS Institute Inc., Cary, NC).

RESULTS

The median age of 983 patients who underwent AHCT between August 2006 and December 2010 was 58 years (range, 19 to 77), of which 61% were male. Among these patients, 41% had myeloma, and, together with amyloidosis and Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes (POEMS), plasma cell disorders were the indication for transplantation in 58% of patients, followed by lymphomas (40%), and acute leukemia (2%) (Table 1). Eighty-two patients (8.3%) had a prior history of arrhythmia, and 38 (3.9%) had a history of arrhythmia during the month before transplantation. Eighteen patients (.2%) had AF or flutter at the start of transplantation. Two hundred seven patients (21.1%) were on a beta-blockers, and 24 (2.4%) were on verapamil or diltiazem at the time of AHCT. The median estimated duration to dismissal from outpatient area to home hematologist (home-dismissal) post-transplantation was 19 days (95% confidence interval [CI], 19 to 20). Overall, 29 patients (3%) died during the 100 days posttransplantation due to infectious causes, multiorgan failure, pulmonary complications, and progressive disease in 15 patients and infection, multiorgan failure syndrome, acute respiratory distress syndrome, and thromboembolic complications in the remaining 14 patients.

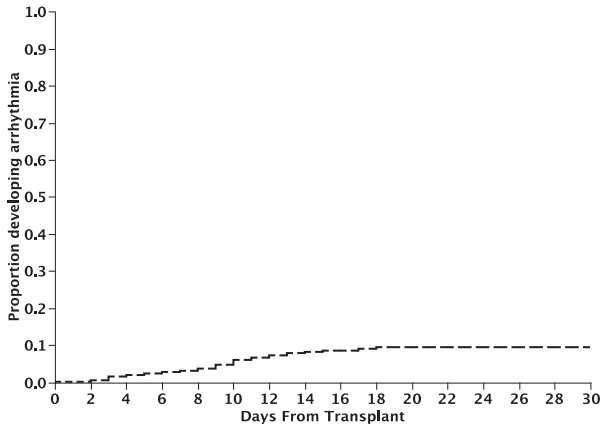

Figure 1. Time to onset of arrhythmia posttransplantation (Kaplan-Meier estimate).

Overall, 92 patients (9.4%) developed a symptomatic supraventricular arrhythmia during the stem cell transplantation course, at a median of 9 days posttransplantation (range, 0 to 18). The cumulative incidence of symptomatic arrhythmia in the posttransplantation period is shown in Figure 1 (Kaplan-Meier estimate). AF was the most common and was seen in 71 patients (7%), followed by atrial flutter in 12 (1%) and supraventricular tachycardia in 8 (1%) (Table 2).

Table 2
Arrhythmia Characteristics (n = 92)

Characteristics	N	Percent
Arrhythmia onset, BMT day (range)	9 (0-18)	
Duration, mean (range)	<1 day (<1 to 17 days)	
Type of arrhythmia		
AF	71	78
Atrial Flutter	12	13
SVT	8	8
MAT	1	<1
Management		
Treatment required	82	89
Beta-blockers	68	74
Calcium channel blockers	40	43
DC cardioversion	7	8
Outcome		
Hypotension	33	36
Vasopressors	13	14
Recurrence	23	25

BMT indicates bone marrow transplantation; SVT, Supraventricular Tachycardia; MAT, Multifocal Atrial Tachycardia; DC, Direct Current.

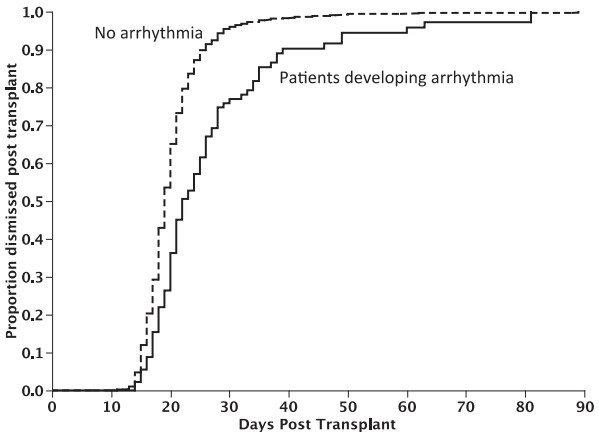

Figure 2. Median time to dismissal home after transplant (Kaplan-Meier estimate). The median time to dismissal after transplant for patients developing an arrhythmia was 22 days as compared with 19 days for those who did not develop an arrhythmia ($P < .001$).

One patient developed multifocal atrial tachycardia. The rhythm had normalized in 81 patients (88%) at the time of dismissal posttransplantation, with a median duration of arrhythmia of less than 1 day (range, <1 to 17 days). Eighty-two patients 82 (89%) developing arrhythmia required treatment, with most of them receiving a beta-blocker and/or calcium channel blocker. Thirty-six percent of the patients with an arrhythmia developed hypotension, but only 14% required vasopressor support and 8% were electrically cardioverted during the peritransplantation period. Twenty-three patients (25%) had recurrence of their arrhythmia before dismissal at a median time of 12.5 days (range, 5 to 21). The median time to dismissal after transplantation for patients developing an arrhythmia was 22 days as compared with 19 days in those who did not ($P < .001$) (Figure 2).

We then examined various pre and peritransplantation clinical and laboratory parameters to identify risk factors for onset of supraventricular arrhythmias. In a univariate analysis, older age, presence of supraventricular complexes or AV conduction delays such as first -or second-degree AV block on pretransplantation ECG, presence of any valvular abnormality, presence of premature atrial complexes on ECG pretransplantation, increased atrial size, history of hypertension, history of CAD, any prior history of arrhythmia, or being on a beta-blocker or antiarrhythmic agent all increased the risk of developing a supraventricular arrhythmia after transplantation (Table 3). We specifically examined the relation between amyloid heart disease and risk of developing arrhythmia. Although there was a trend toward increased risk in the presence of amyloid heart disease, this was not significant ($P = .08$).

Using logistic regression, the best cut-off for age and for atrial size in terms of risk of developing arrhythmia was 63 years and 33 cc/m^2. However, in a multivariate analysis, only age older than 63 years, presence of supraventricular complexes or AV conduction delays on pretransplantation ECG, and history of any prior arrhythmia increased the risk of arrhythmia during transplantation. Among the patients with age older than 63 years, presence of supraventricular complexes or AV conduction delays on pretransplantation ECG, and history of any prior arrhythmia, 20%, 26%, and 23%, respectively, developed an arrhythmia compared with 4%, 8%, and 8%, respectively, among those without the risk factors ($P < 0.001$ for each of the three comparisons). Patients with 2 or more risk factors were at 12.7-fold (95% CI, 6.7 to 24) and those with 1 risk factor at 6.4-fold (95% CI, 3.8 to 11.3) higher risk of developing arrhythmia compared with those with no risk factors (Figure 3). None of the underlying hematological malignancies or medical comorbidities impacted the risk of developing arrhythmia.

DISCUSSION

Supraventricular arrhythmias are a well-recognized complication after hematopoietic stem cell transplantation [6-9]. The incidence of these complications was 9% in this study, which is consistent with the previously reported incidence of 4% to 10% [6-9]. However, none of the studies so far, including ours, had patients on continuous cardiac monitors, so the true incidence may be even higher.

AF was the most common arrhythmia and was present in about 77% of patients developing an arrhythmia. The median time at onset of arrhythmias was 9 days after AHCT, and this is slightly later than the onset of between 3 and 7 days as reported by earlier studies [6,8,9]. Most arrhythmias were short lasting, however, with median duration of less than a day. Interestingly, one fourth of these patients had a recurrence of the arrhythmia at a median of 12.5 days, but most patients (88%) were discharged in sinus rhythm. Although a difference in mortality was not seen, these arrhythmias were associated with an increase in the median time to dismissal home from outpatient follow-up by 3 days.

Although well known, studies evaluating risk factors for these arrhythmias are scarce. Most studies done so far have

Table 3
Univariate Comparisons of Patients with or Without Arrhythmia

Characteristics	Arrhythmia (n = 92)		Control Subjects (n = 891)		Risk Ratio (95% CI)	*P*
	N	Percent	N	Percent		
Age > 63 yr	**62**	**67**	**246**	**28**	**4.8 (3.2-7.6)**	**<.0001**
Prior history of arrhythmia	**19**	**20**	**63**	**7**	**3.2 (1.9-5.2)**	**<.0001**
History of hypertension	47	51	325	36	1.7 (1.1-2.6)	.01
History of CAD	15	16	60	7	2.5 (1.4-4.2)	.003
Beta-blockers/antiarrhythmic at transplant	31	34	183	21	1.9 (1.2-3.0)	.005
Electrocardiographic features						
AV conduction delay or premature supraventricular complexes	**17**	**18.5**	**49**	**5.5**	**3.2 (1.8-5.4)**	**.0002**
Echocardiographic characteristics						
Atrium > 33 cc/m^2	49	54	304	35	2 (1.3-3.1)	.0008
Presence of valvular abnormalities	12	13	55	6	2.2 (1.1-3.9)	.02

Cox proportional hazards models. Bolded rows indicate variables significant in multivariate analysis.

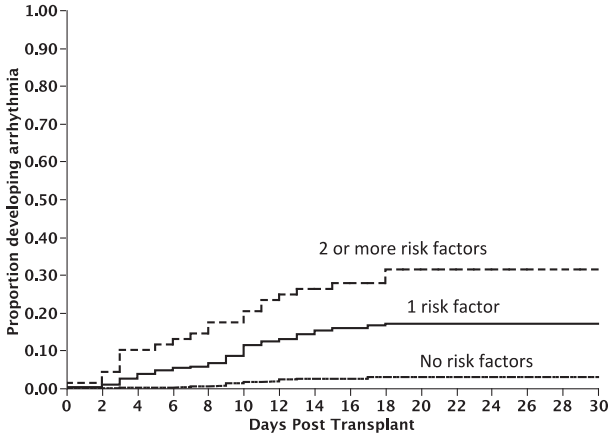

Figure 3. Risk factors predicting development of arrhythmia post-transplantation. Cumulative incidence curves for onset of arrhythmia after transplant are shown. Patients with 2 or more risk factors were at 12.7-fold (95% CI, 6.7 to 24) and those with one risk factor at 6.4-fold (95% CI, 3.8 to 11.3) higher risk of developing arrhythmia compared with those with no risk factors.

implicated older age and the presence of cardiac dysfunction in predisposition to this risk [6,7,9]. Even in the general population, the risk of developing AF increases with age, with approximately 70% of patients with AF between ages 65 and 85 years [12]. Statistical analysis of our results showed age older than 63 as a major risk factor, with a risk ratio of 4.8.

Another predisposing factor emphasized in the multiple studies is the use of chemotherapeutic agents. Among the agents currently in use in transplantation patients, the association of melphalan with AF is the most well established and has been implicated in a significant proportion of patients, including those without any structural or functional cardiac defects as well as those who are young [10]. Studies have shown melphalan use to be associated with AF in 6.6% to 11% of bone marrow transplantation patients, which is significantly higher than any other chemotherapeutic agent [9,13-15]. Our study cohort was mainly composed of patients with plasma cell disorders or lymphoma as the indication for transplantation in most, and thus melphalan-free regimens were given in only a few patients. Hence, the role of melphalan could not be ascertained from our study.

History of arrhythmias was another predisposing factor we observed in this study. Surprisingly, being on an antiarrhythmic agent was shown as a risk factor but only on univariate analysis. This may reflect identification of those with history of arrhythmias. A predominance of older patients in our study with multiple comorbidities requiring the use of these agents may explain this finding. Similarly, factors such as increased atrial size and history of hypertension or CAD were found to be significant on the univariate model but not on the multivariate model. It is possible that all these risk factors are inter-related and may be predisposing to atrial arrhythmias even before the transplantation.

More than one-half of our study group patients had a plasma cell disorder. Whether the presence of cardiac amyloidosis in these patients predisposes to arrhythmias has always been a question. We found that although a higher percentage of patients who developed supraventricular arrhythmia had evidence of cardiac amyloidosis by echocardiogram than the control subjects, the results were not statistically significant. However, at the same time, it must be kept in mind that sensitivity of echocardiograms to detect early cardiac involvement in amyloidosis tends to be low even with recent advances [16-18].

Electrocardiographic changes such as AV conduction delays (first- or second-degree blocks) and Premature atrial contractions were present in about 7% of patients during the pretransplantation period, and their presence independently predicted atrial arrhythmias posttransplantation. Both frequent Premature atrial contractions and AV conduction abnormalities have been previously shown to predict new AF in the general population [19,20]. Several studies have demonstrated the association between delayed intra-atrial or interatrial conduction and increased risk of AF [21-23]. Although first-degree AV block usually involves conduction delay in the AV node, it is frequently accompanied by abnormalities in other parts of the conduction system. In addition, a prolonged PR interval can lead to delayed and ineffective mitral valve closure and diastolic mitral regurgitation, especially when the PR interval exceeds 230 ms. Early asymptomatic cardiac amyloidosis predisposing to AV conduction problems as well as posttransplantation AF could be a possibility that will need further investigation [24-26]. Meanwhile, the presence of asymptomatic conduction blocks or superior vena cava (SVC) on ECG even before stem cell transplantations should not be disregarded.

In conclusion, among patients undergoing autologous peripheral blood stem cell transplantation, the risk of developing a supraventricular arrhythmia in the peri-transplantation period is approximately 9%. The risk is higher among older patients, those with a prior history of arrhythmias, and those with electrocardiographic abnormalities suggesting AV conduction delay and premature supraventricular complexes. Although no association with increase in mortality has been shown, these arrhythmias may warrant additional management and can increase the time to discharge, thereby increasing the cost of care. Identification of these high-risk patients may allow development of specific interventions in future.

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